KI REPORTS
KIReports.org

The Discordance Between the Renal Histopathology and Clinical Presentation of Diabetic Nephropathy Calls for Novel Approaches for the Prediction and Monitoring of Kidney Failure in Diabetes

Jakob A. Østergaard[1,2,3] and Mark E. Cooper[3]

[1]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; and [3]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia

Kidney Int Rep (2021) **6,** 2258–2260; https://doi.org/10.1016/j.ekir.2021.07.029

See Clinical Research on Page 2392

Advances in our understanding of the pathogenesis of diabetic nephropathy are severely hampered by our limited knowledge as to how kidney histopathological changes mirror clinically available markers, such as urinary albumin excretion and estimated glomerular filtration rate and vice versa. A significant obstacle in this regard has been the low number of renal biopsy specimens obtained in clinical practice as part of diagnosing and monitoring diabetic nephropathy. This is particularly relevant over the last 20 years when most clinicians have considered the limited gain and potential risk of performing kidney biopsies. Thus, in clinical practice, the diagnosis of diabetic nephropathy has remained mostly based on the clinical course of the renal impairment where diabetes duration, glycemic control, and the presence of other complications are key factors when considering if the renal disease is due to diabetes *per se*. By contrast kidney biopsies are usually restricted to the setting of atypical clinical presentations where there is uncertainty as to the etiology of the kidney impairment, even in the presence of diabetes.

In the article "Renal Histology in Patients with Type 2 Diabetes, Normoalbuminuria, Microalbuminuria or Proteinuria, Normal or Reduced Renal Function: The Hidden Role Of Vascular Lesions" featured in this issue of *Kidney International Reports*, Rodríguez *et al.*[1] present their evaluation of a unique set of renal specimens obtained from nephrectomy specimens of 90 patients. In their study, the much larger samples than seen with a routine renal biopsy allow for the examination of about 170 glomeruli per patient, including vascular tissue. The authors aimed to help fill the important knowledge gap in our understanding of the relationship between renal histopathology and clinical markers of kidney disease. This study confirms the dissociation between the clinical presentation of kidney function and renal histopathology. This is consistent with previous reports, including the seminal study by Fioretto *et al.*[2] Furthermore, this study has also revealed widespread vascular disease including in patients with preserved kidney function as well as in those with normal urinary albumin excretion as previously reported in a recent Japanese study.[3]

As a consequence of the kidney specimens obtained in the present study including a broader representation of glomeruli and vascular tissue, Rodríguez *et al.*[1] were able to show with greater accuracy the glomerular and vascular histopathology in patients across the clinical spectrum of chronic kidney disease stages. Thus, this study has highlighted that estimated glomerular filtration rate and urinary albumin excretion often fail to reveal developing kidney structural lesions. The authors found that patients with normal urinary albumin excretion frequently have advanced glomerular, tubular, as well as interstitial injury. For example, 10% to 20% of the patients with normal urinary albumin excretion had nodular glomerulosclerosis (class III diabetic nephropathy) as well as tubular lesions with atrophy, fibrosis, and inflammation. In addition, many patients with

Correspondence: Mark E. Cooper, Department of Diabetes, CCS, The Alfred Centre, Level 5, 99 Commercial Road, Melbourne, VIC 3004 Australia. E-mail: mark.cooper@monash.edu

macroalbuminuria only had mild structural injury within the kidney. These changes may explain the dissociation frequently seen between urinary albumin excretion and kidney function, including why some diabetic patients lose kidney function despite not developing proteinuria.[4]

The study importantly also unmasked extensive vascular damage in patients with type 2 diabetes which was present even among patients with normal urinary albumin excretion and preserved estimated glomerular filtration rate. Of particular interest, 80% to 100% of the cases were found to have moderate hyalinosis and arteriolar sclerosis including in patients with normo- and microalbuminuria. Furthermore, these vascular lesions were seen across the diabetic nephropathy histopathological classes I, II, and III. The same moderate degree of tubular atrophy, interstitial fibrosis, and inflammation was observed across cases with class IIa, IIb, and III diabetic nephropathy. Thus, it is possible that renal vascular damage leads to these changes via ischemia independently of glomerular damage.

The study adds knowledge to our understanding of diabetic nephropathy. However, the study has important limitations in part due to its cross-sectional design and recent developments in clinical practice regarding the changes in the use of glucose-lowering drugs. The histopathological impact of pharmaceutical interventions targeting disease development of diabetic nephropathy including the renin-angiotensin-aldosterone system blockade (which was administered to 58%, 64%, and 76% of patients with normo-, micro-, and macroalbuminuria, respectively) therefore remains to be clarified. In addition, the impact of glucagon-like peptide 1–receptor agonists and sodium glucose cotransporter 2 inhibitors cannot be assessed in the present study as only a few patients were treated with these drugs; yet in the contemporary management of type 2 diabetes, these newer drug classes are increasingly being recommended to those subjects with or at risk for diabetic kidney disease. Furthermore, only a few cases in the study were diagnosed with diabetic retinopathy, that is, 3%, 6%, and 20% of the patients with normo-, micro- and macroalbuminria, respectively. The diagnosis of diabetic retinopathy was based on existing medical records and the low prevalence is therefore most likely due to a low level of detection rather than an effect of selection bias with retinopathy commonly associated with increased renal disease in most rigorous epidemiological studies in type 2 diabetes.

Another cause of concern is the inability by study design to distinguish diabetes-related effects on kidney histopathology from those related to normal age-related effects on the kidney. In a subanalysis of the data, the authors compare cases involving patients aged more than 60 years old with those younger than 60 years old and noted that a higher fraction of the evaluated glomeruli exhibited total sclerosis (8%) in the older group as compared with the younger group (4%). Likewise, more patients in the older group had moderate fibrointimal thickening (89%) compared with the younger patients (67%) as evidence of arteriosclerosis. The authors concluded that these numbers are high and clinically relevant despite the differences between age groups and in part could reflect a diabetes-induced acceleration of the age-related kidney changes as previously suggested by others.[5]

With this study, Rodríguez *et al.*[1] has added important knowledge to our understanding of diabetic nephropathy through their thorough and systematic evaluation of high-quality sections from nephrectomy specimens in patients with type 2 diabetes. The data indisputably have illustrated the complexity of the disease and the intriguing yet perplexing discordance between the clinical presentation of diabetic nephropathy and renal histopathology. This study has further highlighted our need for better tools for noninvasive prediction of kidney damage in diabetes. Future studies must investigate how novel markers of diabetic nephropathy mirror histopathology and disease progression. As emphasized by the authors, the results call for the application of novel unbiased approaches to assess renal pathology including urinary peptidomics, liquid-biopsies, and magnetic resonance imaging of renal microstructure, oxygenation, and metabolism.[6,7]

DISCLOSURE

The authors have declared no competing interests.

REFERENCES

1. Rodrigues R. Renal histology in patients with type 2 diabetes, normoalbuminuria, microalbuminuria or proteinuria, normal or reduced renal function: the hidden role of vascular lesions. *Kidney Int Rep*. 2021. In press.
2. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia*. 1996;39:1569–1576.
3. Furuichi K, Shimizu M, Hara A, et al. Diabetic nephropathy: a comparison of the clinical and pathological features between the CKD risk classification and the classification of diabetic nephropathy 2014 in Japan. *Intern Med*. 2018;57:3345–3350.
4. MacIsaac RJ, Ekinci EI. Progression of diabetic kidney disease in the absence of albuminuria. *Diabetes Care*. 2019;42:1842–1844.
5. Guo J, Zheng HJ, Zhang W, et al. Accelerated kidney aging in diabetes

mellitus. *Oxid Med Cell Longev*. 2020;2020:1234059.

6. Magalhaes P, Pejchinovski M, Markoska K, et al. Association of kidney fibrosis with urinary peptides: a path towards non-invasive liquid biopsies? *Sci Rep*. 2017;7:16915.
7. Selby NM, Blankestijn PJ, Boor P, et al. Magnetic resonance imaging biomarkers for chronic kidney disease: a position paper from the European Cooperation in Science and Technology Action PARENCHIMA. *Nephrol Dial Transplant*. 2018;33:ii4–ii14.